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Title: Clozapine rechallenge following neuroleptic malignant syndrome -a systematic review

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Title: Clozapine rechallenge following neuroleptic malignant syndrome -a systematic review

Running title:
Clozapine rechallenge & NMS

Purpose/Background

Neuroleptic malignant syndrome (NMS) has been described with most antipsychotics, most commonly first generation. Clozapine has also been associated with NMS.

Methods/Procedures

We conducted a systematic review to identify all studies investigating or describing (a) clozapine rechallenge following suspected NMS associated with clozapine, (b) clozapine

use after suspected NMS associated with another antipsychotic, and (c) rechallenge with non-clozapine antipsychotics after suspected clozapine associated NMS.

Findings/Results

We identified 51 reports detailing 67 cases. Thirty-eight described clozapine administration after NMS on a non-clozapine antipsychotic, 12 a clozapine re-challenge after a NMS on clozapine monotherapy, and 17 described the use of non-clozapine antipsychotics after a NMS on clozapine.

The outcome of clozapine rechallenge was favourable (no recurrence of NMS) in 92% (n=11) of cases after a NMS on clozapine and in 79% (n=30) of those prescribed clozapine following NMS on a non-clozapine antipsychotic. Most (82%; n=14) cases after NMS on clozapine had no recurrence of NMS on receiving a non-clozapine antipsychotic.

No mortality was reported with any of these interventions.

Implications/Conclusions

Our findings suggest that rechallenge following clozapine NMS is possible, and with careful risk/benefit analysis consideration, a clozapine rechallenge can be made. A publication bias in favour of cases in which rechallenge was successful is probable and is an important limitation.

Keywords: NMS; antipsychotic; adverse events; CK; fever; rigidity;

Word count: 3300

Abstract 209

Manuscript:

Introduction

Recovery in psychotic disorders remains suboptimal.¹ Clozapine remains the only evidence based effective treatment for the 30% of schizophrenia cases with treatment

resistance,² with up to 70% of patients responding.^{3,4} There are no effective treatments for the 30% of treatment resistant patients who fail to respond to clozapine or in those when clozapine is discontinued due to adverse events.

The use of first generation antipsychotics (FGAs) with high dopamine receptor-2 blockage is associated with an incidence of neuroleptic malignant syndrome (NMS) as high as 0.2%,⁵ while more recent data suggests an incidence of 0.01-0.03% in people treated with second generation antipsychotics, including clozapine.⁶⁻⁹

Earlier reviews evaluating NMS associated with clozapine, described the associated clinical characteristics¹⁰⁻¹⁵ and compared clozapine associated NMS with NMS due to FGAs.^{10, 13}

The general advice following an episode of NMS is that subsequent treatment should be with structurally different preparations. Given the lack of effective alternatives to clozapine for those patients who develop a clozapine-associated NMS, there are no evidence-based effective treatments. Hence, a review of clozapine use following clozapine NMS is required to assess the safety of the treatment intervention. Further, the use of clozapine following NMS associated with non-clozapine antipsychotics, and the safety of alternative antipsychotics following clozapine-associated NMS, has not been systematically evaluated to date.

The purpose of this review is to assess the safety of clozapine use, or alternative antipsychotic use following an episode of clozapine-associated NMS. We will also evaluate the outcomes of clozapine in antipsychotic rechallenge following NMS associated with non-clozapine antipsychotics.

Methods

We performed a literature search to identify peer-reviewed interventional and observational studies, case series and case reports until July 2018, investigating or describing rechallenge following clozapine-associated NMS (with clozapine or a non-clozapine antipsychotic rechallenge) or clozapine use after an episode of non-clozapine antipsychotic associated NMS. This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) standard.¹⁶

Inclusion criteria

Studies and case reports of patients (no age restrictions) who had a clozapine monotherapy rechallenge following a diagnosis of clozapine associated NMS or of non-clozapine antipsychotic associated NMS; or in which a non-clozapine antipsychotic was used after an episode of clozapine associated NMS, including patients who had a clozapine associated index NMS with a prior history of NMS (see supplementary files 1-3 for a list of included studies).

An episode of NMS was diagnosed according to the definition applied in the individual cases or studies.

Exclusion criteria

Studies were excluded if: 1) the index NMS episode occurred with the use of a second antipsychotic medication concurrent to clozapine therapy (please see supplementary file 4 for a list of these excluded studies);

Information sources and searches

Two independent reviewers (JL and CM) performed an electronic search using PubMed, Medline, Scopus, EMBASE and Google Scholar from inception until July 2018 with no language restrictions. The following search terms were used, alone and in combination: “Neuroleptic malignant syndrome” and “clozapine”. In addition, the reference lists of the retrieved articles and relevant review articles were hand-searched for further reports.

Study selection and exclusion

All extracted reports were examined independently by two authors (JL and CM), and a list of full text articles established. We planned to contact authors for clarification where necessary, but this was not required.

Outcomes

In this review we sought to identify cases in which 1) clozapine or 2) an alternative antipsychotic was used during rechallenge following clozapine associated NMS and; 3) to describe the use of clozapine following NMS secondary to a different antipsychotic. The outcomes were the proportions of successful rechallenges in each of the circumstances listed above. A successful rechallenge was defined as a rechallenge with no evidence of recurrence of NMS within the reported timeframe.

We also recorded the clinical characteristics of the index NMS episode, and NMS episodes that occurred on rechallenge (either with clozapine or with an alternative antipsychotic). We provided descriptive summaries of the course of NMS (time to onset

of the NMS episodes; described duration of NMS episode; nature of NMS symptoms; treatments used; and mortality).

Data extraction

We extracted information on the course, signs and symptoms of NMS. If the study authors made no reference to a symptom, sign, laboratory value or timeframes, then they were coded as missing. The following information was extracted where possible:

- 1) demographic and clinical characteristics of patients (gender, age, ethnicity and primary diagnosis)
- 2) rechallenge with clozapine or a non-clozapine antipsychotic and interval between index NMS episode and rechallenge
- 3) clinical outcome: Recurrence of NMS and/or death and duration of follow up.
- 4) mean clozapine /antipsychotic dose(mg/d) at the time of the index NMS event and during rechallenge; duration of treatment with clozapine / antipsychotic therapy prior to onset of NMS (index or rechallenge episode); available plasma clozapine concentrations at the time of the NMS.
- 5) we established the day of onset of NMS as described by the authors of the case, and where not specified, the day when NMS symptoms began was defined as the start of the NMS episode. Time to recovery from NMS was that specified by the study authors, or if not reported: the time to 1) resolution of NMS symptoms, or 2) normalisation of CK levels.
- 6) we extracted data on clinical symptoms at the index NMS episode including: mild fever (37 – 37,9°C), fever >38°C, extrapyramidal symptoms, (including tremor, rigidity) ; altered mental status, (including sedation or somnolence, disorientation, confusion, disorganization), autonomic symptoms and signs (including tachycardia, hypertension, labile blood pressure, sweating, urinary incontinence) and; laboratory data (including: reported creatine kinase (CK) elevation, CK level; reported White Blood Cell (WBC) elevation, WBC level).
- 7) agents used to treat NMS.

Results

Study selection, study and participant characteristics

The study selection process, search results, and reasons for exclusion are given in figure 1.

The initial search yielded 1049 references after removal of duplicates. After checking titles and abstracts, 134 full texts were assessed for eligibility and 51 of these (n=67 patients) included for data extraction. All were case series (n=7) or case reports (n=44); no interventional or observational studies were identified.

Of the 67 cases, 12 were a clozapine rechallenge after a clozapine associated NMS, 17 cases were the use of non-clozapine antipsychotics after a clozapine associated NMS and 38 were the use of clozapine after a non clozapine antipsychotic associated NMS (supplementary files 1-3). The characteristics of the index NMS episodes are shown in table 1.

NMS recurrence rate

The recurrence rate of NMS on re-challenge for the entire sample was 12/67 (18%). The recurrence rate, either with re-challenge using clozapine (9/50 (18%)) or non-clozapine (3/17 (18%)), is the same. The recurrence rate for index NMS with clozapine was 4/29 (14%) and for index non-clozapine NMS was 8/38 (21%).

Clozapine associated NMS and clozapine rechallenge

The outcome of clozapine rechallenge was favourable in 92% (n=11) cases after a clozapine associated NMS. No patients died following a clozapine rechallenge.

Clozapine use after a non-clozapine antipsychotic associated NMS

The outcome of clozapine rechallenge was favourable in 79% (n=30) cases after a non-clozapine antipsychotic associated NMS. No mortality was associated with this. Of those cases in which clozapine rechallenge was unsuccessful (n=8), only one case reported subsequent use of antipsychotic medication, with a recurrence of NMS with risperidone use, and a subsequent successful rechallenge with quetiapine 400mg daily, with no NMS recurrence at 6 months.¹⁷ Two cases were treated with ECT alone,¹³ one of which was treated with maintenance ECT,¹⁸ while other cases with a history of bipolar affective disorder were treated with mood stabilizers, lithium carbonate and carbamazepine.¹⁹⁻²¹

Clozapine associated NMS and non-clozapine antipsychotic use on rechallenge

The outcome of rechallenge with a non-clozapine antipsychotic was successful in 82% (n=14) of cases after a clozapine antipsychotic associated NMS. No cases reported a death with rechallenge.

The demographic and clinical characteristics of the rechallenge episode following an index NMS episode are shown in table 2.

Clozapine associated NMS and rechallenge

No plasma clozapine concentrations were documented in the index NMS. There was no significant difference in the rate of successful challenge with the use of clozapine (92%; n=11) or non-clozapine antipsychotics (82%; n=14 successful rechallenges) after a clozapine associated index NMS ($\chi^2=0.513$, $p=0.622$). The duration from index NMS to rechallenge was significantly longer for those rechallenged with clozapine (mean =93.7 (SD=96.0) days) than those rechallenged with a non-clozapine antipsychotic (mean=22.4 (SD=26.8) days) ($t=2.562$, $p=0.019$).

Unsuccessful rechallenge after index NMS episode

Clinical and demographic characteristics of those cases with an unsuccessful rechallenge are shown in table 3. Only one case of clozapine rechallenge after a clozapine associated NMS was unsuccessful, with a recurrence of NMS.²²

Twenty one percent (n=8) of cases of clozapine use after a non-clozapine antipsychotic NMS index episode;^{13, 17-21, 23} and 18% (n=3) of cases with non-clozapine antipsychotic use after an index clozapine associated NMS were associated with a recurrence of NMS.²⁴⁻²⁶

There was no significant difference in the rate of NMS recurrence between those treated with clozapine (8%; n=1) and those treated with non-clozapine antipsychotics (18%; n=3) after an index clozapine associated NMS episode.

NMS recurrence with clozapine rechallenge

There was one case of a recurrence of NMS with clozapine rechallenge in a 61 year old male.²² In this case the index clozapine associated NMS occurred after 30 years of clozapine use and was associated with a peak CK level of 33521 IU/L. Clozapine rechallenge occurred at 14 days after the index episode, and was associated with a rapid rise in CK to 5505.0 IU/L within one day of clozapine rechallenge. The other clozapine associated index NMS cases (n=21) had a mean time to NMS onset of 754.2 (SD=1352.3) days. The mean time to clozapine rechallenge in other clozapine NMS cases was 103.6 (SD=97.5) days (range 8-270 days).

Of all the episodes of NMS recurrence with clozapine use during rechallenge (n=1 following a clozapine associated NMS and n=8 following a non clozapine antipsychotic

associated NMS episode), there was rigidity recorded in 86% of cases (n=6 (with n=1 case of clozapine use following clozapine associated NMS)).

The use of clozapine following non-clozapine antipsychotic NMS was associated with recurrence of NMS in 21% of cases. There was a significant difference in time to rechallenge with clozapine in non-clozapine associated NMS cases between those with a successful clozapine use (mean time to clozapine use after index non-clozapine associated NMS (mean=25.6 (SD=58.20) days) and those who had a recurrence of NMS with clozapine use (mean=227.5 (202.1) days) ($t=-2.872$, $p=0.013$). There was no significant difference in duration of index NMS between those with a successful clozapine use (mean duration=8.4 (5.2) and a recurrence of NMS (mean=9.8 (SD=8.7) days) ($t=-0.399$, $p=0.694$) nor was there a higher use of bromocriptine and/or dantrolene in those with a successful clozapine use (48% (n=10)) and those with an NMS recurrence (50% (n=2)) ($\chi^2=0.008$, $p=0.672$).

Discussion

In this review, over 90% of patients are reported to have been successfully rechallenged following a clozapine associated NMS; when clozapine was used after an NMS associated with a non-clozapine antipsychotic, the success rate was 79%. The use of alternative antipsychotics following a clozapine associated NMS was still associated with a high success rate of 82% with no recurrence of NMS; though whether or not patients had a clinical response and remission of psychotic symptoms is not clear. Given the lack of evidence supporting effectiveness of non-clozapine antipsychotics in TRS, this provides support to consider clozapine in rechallenge.

Successful rechallenge and NMS recurrence

The literature is limited by case reports which do not provide comprehensive detail on the use of antipsychotic rechallenges after an episode of NMS.⁷ The recurrence rate following NMS may be as high as 30%,⁵ with an early literature review of 40 rechallenges identifying a NMS recurrence rate with FGAs as between 13% (confirmed) and 37% (likely) cases.²⁸ We identified an overall recurrence rate of 18% with the use of clozapine following NMS, with a recurrence rate of 8% when used following clozapine NMS, and 21% following non-clozapine NMS.

Where clozapine associated NMS is the index episode, characteristics of the NMS

episode were in keeping with those identified in previous reviews. Rigidity was present in 77% of clozapine associated index NMS episodes, in keeping with a previous review which highlighted that the absence of rigidity was not a differentiating characteristic between clozapine and FGA associated NMS.¹⁵ The higher prevalence of tremor in NMS associated with non-clozapine antipsychotics may be due to the presence of non-specific extrapyramidal effects associated with FGAs in particular, as tremor is not recognised as a salient feature of NMS.²⁹ Where an unsuccessful rechallenge with clozapine occurred, 86% had evidence of rigidity as a feature of NMS recurrence.

The only published unsuccessful case of clozapine rechallenge following clozapine NMS was a somewhat atypical presentation, with an onset of NMS at 30 years following clozapine initiation²² (compared to an average duration to NMS onset of 2.1 years for other clozapine NMS cases identified in this review). This unusual timing of NMS onset raises the question of diagnostic specificity, and the possibility that other factors may be responsible for an NMS type presentation. The time to clozapine rechallenge was only 14 days in this case, compared to the average 125 days (range 8-270 days) reported for successful clozapine rechallenge in 8 other cases of clozapine NMS (2 of which had a successful clozapine rechallenge with clozapine initiation within 10 days of the index episode). Unsuccessful clozapine use after a non-clozapine NMS use was associated with an onset of NMS after an average of 103 days (range 1-450 days). What can be drawn from these data is that recurrence of NMS following clozapine rechallenge can occur at a wide variety of durations, and continued vigilance is required, particularly in the first year of treatment. Increased vigilance for the occurrence of autonomic symptoms, including tachycardia, tachypnea and blood pressure lability is warranted during clozapine rechallenge as these symptoms are more common and severe in clozapine NMS.¹⁴

Time to clozapine or antipsychotic use following clozapine NMS

The median time to rechallenge with clozapine use after a clozapine associated NMS was 90 days, and it was 14 days with the use of a non-clozapine antipsychotic-this is largely explained by two case reports with a duration to clozapine rechallenge of 180 days each^{30, 31} and one case with a duration of 280 days.²⁶ One of these cases reported a trial discontinuation of antipsychotic medications before clozapine use,³¹ and the other two did not comment on whether antipsychotic medication was used or not prior to clozapine rechallenge. This pattern makes sense as the current guidance for

rechallenge following NMS is to try to use an antipsychotic structurally unrelated to the one which was believed to have provoked the NMS. But where clozapine is the only effective antipsychotic, it may need to be trialled again, once other options have been considered.

Time to clozapine use in non-clozapine NMS

For non-clozapine antipsychotic associated NMS, it may be that the choice of antipsychotic is not the primary factor in risk of recurrence, but instead that the duration between the index episode of NMS and rechallenge is key⁷. When clozapine was used after a non-clozapine associated NMS episode, the average delay was 22.4 days to the initiation of clozapine. Those with a successful clozapine use, and no recurrence of NMS had a significantly reduced time to clozapine initiation compared to those with an unsuccessful rechallenge (in NMS recurrence 4 cases had at least one other antipsychotic trial prior to clozapine use (2 cases with one, 1 case with two, and a case with four antipsychotic trial(s)). This was not accounted for by an increased clinical severity or a longer course of index NMS episode in those with a recurrence of NMS.

Severity of index NMS episode

We cannot confirm the accuracy of the diagnoses of the index NMS episodes, and there are, for example, other causes of high CK. Instead therefore, we looked at markers of severity of the clinical picture. A proxy measure for severity is the range of interventions used to treat the index NMS. Did the patients with a clozapine associated NMS have a less severe index presentation, which may have partially explained the high rate of successful rechallenge? This is not clear from our data; 48% of those with a non-clozapine antipsychotic index NMS were treated with bromocriptine or dantrolene, which was higher than those with a clozapine associated NMS (26%), though the difference did not meet statistical significance.

From the cases reported to date, it is not clear that the high level of successful clozapine rechallenge was not accounted for by less severe (by duration of index NMS or need for bromocriptine and/or dantrolene use).

Limitations

Our findings must be viewed in relation to limitations in the primary study data, and the case review format.

With any case study based review, there is the possibility of publication bias. It is clear that most patients with rechallenge after NMS episodes, and the use of clozapine in rechallenge are not reported in the literature, and it is likely that rechallenge following clozapine NMS and the use of clozapine in rechallenge following NMS is more widely used than is identified here. It is likely that a bias exists towards reporting cases in which there is a successful outcome after clozapine rechallenge.^{33, 34} It may also be possible that cases in which adverse reactions or deaths have occurred are more likely to be reported, but it is unclear if this is pertinent to our review, as no deaths are reported in our rechallenge cases. There is no agreed method to assess the effect of publication bias in case reports. However, since clozapine associated NMS is such a rare condition, case reports provide the only available data to report on the outcomes of clozapine and non-clozapine rechallenge following an index NMS episode. Further while caution is required when interpreting the results, we have included pertinent comparison data between the different rechallenge groups, including duration of the index NMS episode, interventions used to treat the NMS episode, time to rechallenge, and NMS symptoms, factors that are treated differently from one case to the next. We have expanded on the findings of an earlier review which identified 7 cases of clozapine rechallenge (all successful) following NMS, and incorporated data on non-clozapine antipsychotic rechallenge following clozapine associated NMS.

There is no data available on whether rechallenge antipsychotics were successful in achieving remission of psychotic symptoms. As we identified equivalent rates of successful rechallenge between clozapine and non-clozapine antipsychotics in TRS, and given the lack of evidence to support the use of non-clozapine antipsychotics in TRS, this may prioritize clozapine's use over non-clozapine antipsychotics in rechallenge. Finally, as no comparative or observational studies were identified, we are unable to confirm that clozapine rechallenge following NMS or use of non-clozapine antipsychotics following clozapine associated NMS are more likely to be successful than not, with an absence of mortality. There remains a need for caution in interpreting data relating to case reports and case series.³⁵ Case reports alone cannot provide an accurate or quantitative measure of the risk for complications or death associated with a drug or treatment intervention such as this.

Clinical implications

Careful consideration for clozapine rechallenge following an episode of clozapine associated NMS can be made. It should only be considered in cases of treatment resistant schizophrenia. Any clozapine rechallenge should be associated with increased monitoring for evidence of hyperthermia (fever >38 C), rigidity (intractable) (or other extrapyramidal signs, or dysphagia, dysarthria), mental state changes, and autonomic instability. Alongside standard full blood counts, serial measures of CK during the early stages of clozapine use to monitor for NMS would be indicated (though CK is not specific to NMS).

Conclusions

Our findings indicate that successful rechallenge with clozapine after an episode of NMS can be considered, although the probability of underreporting of adverse outcomes must be borne in mind. In using clozapine following NMS, the need for vigilance regarding symptoms of NMS is required, along with a need to be mindful of cumulative antipsychotic dosages and aiming for clozapine monotherapy to reduce the risk of NMS recurrence.

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